Multimodal Neuroprognostication Following Cardiac Arrest

Practical Considerations

Bakhtawar Ahmad, MBBS[a],
Samantha Fernandez Hernandez, MD[b],
Carolina Barbosa Maciel, MD, MSCR[c,d,*]

KEYWORDS

• Neuroprognostication • Outcome prediction • Heart arrest • Cardiac arrest
• Hypoxic-ischemic brain injury • Multimodal prognostication

KEY POINTS

- Neuroprognostication after cardiac arrest involves assessing brain injury burden, cerebral reserve, resilience, and patient values to guide clinical decisions and outcomes.
- Multiple modalities—biochemical markers, neuroimaging, neurophysiologic tests, and clinical examinations—are used to evaluate structural and functional brain injury, each with specific advantages and limitations.
- Challenges include variable guidelines and timing of assessments, limited acess to tools, cognitive biases, and balancing prognostic accuracy with patient values.
- Effective communication with surrogates, emphasizing honesty about uncertainty and understanding patient goals, is crucial for shared decision-making.
- Future directions focus on integrating advanced neuroimaging, concepts of cerebral reserve and resilience, and artificial intelligence to improve prediction accuracy and personalize neuroprognostication.

INTRODUCTION

Neurologic outcome prediction (or neuroprognostication) is a cornerstone of postcardiac arrest care, and in practice, it is the converging lens through which clinical trajectories unfold. Disorders of consciousness (DoC) in the early postcardiac arrest period

[a] Department of Neurology, University of Florida, Gainesville, FL, USA; [b] Department of Neurology, Emory University, Atlanta, GA, USA; [c] Divisions of Neurocritical Care and Epilepsy; [d] Division of Neurocritical Care, University of Florida, Gainesville, FL, USA
* Corresponding author. McKnight Brain Institute, 1149 Newell Drive, Gainesville, FL 32610.
E-mail address: carolina.maciel@ufl.edu

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Abbreviations	
ADC	apparent diffusion coefficient
CPC	Cerebral Performance Category
CT	computed tomography
DoC	disorders of consciousness
DWI	diffusion-weighted imaging
EEG	electroencephalography
FOUR	Full Outline of Unresponsiveness Score
FPR	false positive rates
GCS	Glasgow Coma Scale
GFAP	glial fibrillary acidic protein
GWR	gray-white matter ratio
HIBI	hypoxic-ischemic brain injury
MCS	minimally conscious state
mRS	modified Rankin Scale
NfL	neurofilament light chain
NSE	neuron-specific enolase
PLR	pupillary light reflex
ROSC	return of spontaneous circulation
SSEP	somatosensory evoked potentials

are highly prevalent: It is well known that 8 in 10 patients remain unresponsive to verbal commands following return of spontaneous circulation (ROSC) and deemed to be in a comatose state. Estimating the potential for functional recovery is an essential task in comatose survivors with downstream effects on decision-making that ultimately mediate outcomes. Neuroprognostic impressions uphold decisions for continued life-support and advanced organ-targeted care in patients expected to have favorable outcomes and often guide transitions toward end-of-life care in patients thought to have devastating hypoxic-ischemic brain injury (HIBI). Truly a branching point or a bottleneck in the clinical course; patients, surrogates, and clinicians rely heavily on the accuracy of predictions to guide decisions on whether sustaining life support remains appropriate. An erroneously pessimistic prognosis can cause the death of someone who would have otherwise recovered. An erroneously optimistic impression may, on the other hand, prolong survival in a state that may not align with the patient's wishes in terms of acceptable disability or rehabilitation journey.

Neuroprognostication is *a dynamic process* that begins as early as possible following ROSC. As illustrated in **Fig. 1**, it involves 4 key priority pillars: (a) *overall* burden of brain injury, which includes damage from the initial hypoxic-ischemic insult during cardiac standstill as well as the accrued secondary injury from subsequent insults, neuroinflammation, and programmed cell death despite restored circulation; (b) cerebral reserve; (c) cerebral resilience; and (d) individual patient values regarding acceptable levels of disability and the anticipated recovery journey. Neuroprognostic impressions are formed through the interpretation of findings from all 4 pillars, often within emotionally charged circumstances and in the presence of unavoidable confounders. This is an inherently complex and nuanced process that requires synthesizing multiple data points and critically evaluating the reliability and validity of each finding.

The injury burden is currently evaluated directly or indirectly by guideline-recommended neuroprognostic tools (**Fig. 2**). Biochemical markers of neuronal injury (eg, neuron-specific enolase [NSE]) and neuroimaging assess for direct evidence of structural injury. Neurophysiologic tests and features of the clinical examination evaluate injury burden indirectly through neurologic function. Prognostic impressions reflect the interpretation of test results, considered alongside the severity of the initial

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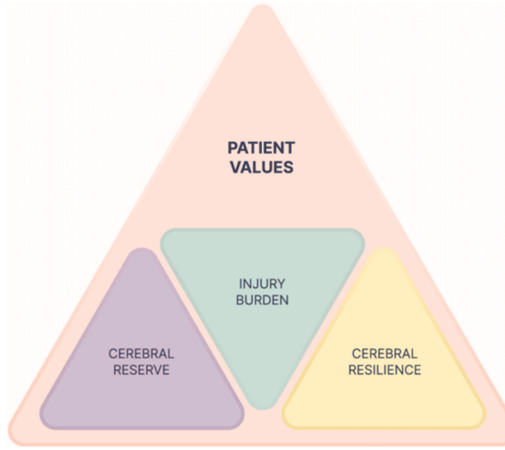

Fig. 1. Key pillars of neuroprognostication.

insult, the extent of accumulated brain injury, and the estimated cerebral reserve. Together, these factors help outline a potential trajectory for recovery. Cerebral resilience and the potential influence of residual confounding can be appraised by noticing mismatches between the perceived severity of cerebral insults and the observed corresponding burden of injury. For instance, minimal injury burden on neuroimaging and preserved neurologic examination despite severe insults suggest a high degree of cerebral resilience. On the same token, low titers of biomarkers and minimal injury on neuroimaging accompanied by ongoing neurologic dysfunction—detected through clinical assessment or neurophysiologic tests—suggest that residual confounding factors may be contributing to the clinical picture. Finally, it is essential to reconcile the projected recovery trajectory with the patient's individual values, as conveyed by their surrogates. These values should serve as the central factor guiding outcomes through shared decision-making. For example, if a prolonged recovery over several

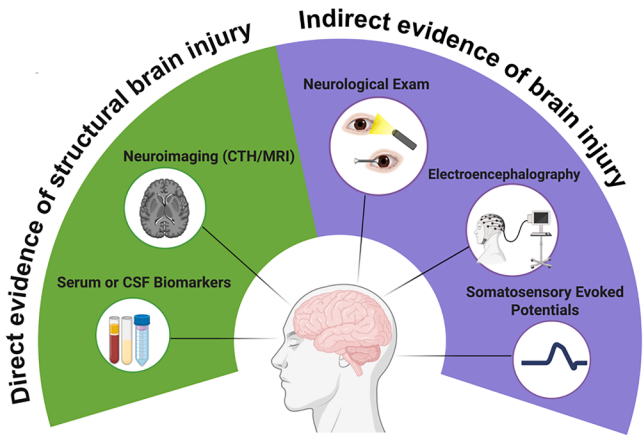

Fig. 2. Components of neuroprognostication.

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months toward functional independence is deemed unacceptable by the patient or their surrogate, then favorable neuroprognostic findings—such as minimal injury burden—become less meaningful, particularly in the context of limited neurologic reserve and a likely extended course of recovery.

Limitations and Challenges of Neuroprognostication

Reconciliation between empirical data and individual values

Estimating early and long-term functional outcomes is not a one-size-fits-all process but rather a dynamic synthesis of multiple factors.[1] These include the nature of acute brain injury, the patient's premorbid state, insights from clinical status and findings from neuroprognostic tests, and ethical considerations, with each factor weighed differently depending on the individual case. The complexity of neuroprognostication following HIBI is further compounded by the significant variability and lack of standardization in current practices despite many different available guidelines.[2–7] While current guidelines outline the evidence supporting the recommendation of each prognostic tool and highlight their pitfalls, they do not prioritize one over another or specify a recommended sequence of use. **Table 1** summarizes the 3 most referenced neuroprognostication guidelines for HIBI; note that American Heart Association 2025 updated version is expected to replace 2020 when published. In practice, clinicians are often faced with the challenge of reconciling conflicting recommendations across existing guidelines and determining how best to apply them to the specific scenario at hand. Even when presented with the same clinical scenario, experts might not agree on their interpretation for the recovery potential and in their final prognostic impressions.[8] Each guideline has their own process for selecting, reviewing, appraising, and synthesizing evidence into a set of recommendations, which include specific norms and boundaries. Most guidelines have limited generalizability, as they are rarely applicable to every possible scenario; their recommendations must remain grounded to the boundaries of available evidence, even while recognizing the disconnect between controlled study conditions and real-world clinical practice. A central practical challenge lies in aligning patient's values regarding acceptable levels of disability with the interpretation of the findings from neuroprognostic tools, as guided by existing recommendations. While the patient's values ultimately define what constitutes a favorable outcome or meaningful recovery—for example, *what level of disability is personally considered unacceptable, and thus, a poor outcome*?—guidelines lack the nuance to accommodate individualized interpretations on a case-by-case basis. Being confined to the available evidence, the meaning behind "poor," "unfavorable," "good," "favorable," "meaningful" in guidelines is derived from the approach chosen by investigators conducting studies that informed practice guidelines. The required pragmatic definitions for analyses, often dichotomizing outcomes from functional scales into "good" and "poor" outcomes, are agnostic of individual premorbid status, preferences, and values. In most neuroprognostic studies, a "favorable" functional outcome is defined by the ability to achieve independence (ie, Glasgow-Pittsburgh Cerebral Performance Category, CPC, scores 1–2 or modified Rankin Scale, mRS, scores 0–3), although some studies have lower thresholds characterized by recovery of consciousness (ie, CPC 1–3 or mRS 0–4). For a cardiac arrest survivor whose premorbid baseline included dependence on others for advanced activities of daily living for the last 2 decades, returning to that baseline state might be a meaningful recovery—yet, without this personalized nuance, this individual is automatically allocated to a category of "poor" outcome in most studies (CPC 3). It is, therefore, essential to recognize this practical limitation when applying recommendations in clinical practice—especially during discussions with surrogates. Rather than focusing solely on

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Table 1
Comparison of neuroprognostication guidelines of cardiac arrest

Guidelines	AHA 2020 Guidelines	ERC-ESICM 2021 Guidelines[1]	NCS 2023 Guidelines
General approach	Delayed, multimodal assessment	Delayed, multimodal assessment	Delayed, multimodal assessment
Pupillary light reflex (PLR)	Bilaterally absent PLR at ≥72 h post-ROSC is a reliable predictor for poor outcome	Same as AHA; recommends quantitative pupillometry if available	Same as ERC-ESICM
Corneal reflex	Bilaterally absent corneal reflexes at ≥72 h post-ROSC/normothermia support poor prognosis	Same as AHA	Cautions against relying on corneal reflex alone
Myoclonus	Status myoclonus within 72 h post-ROSC supports poor prognosis; EEG recommended when myoclonus is present	Same as AHA	Cautions against relying on myoclonus alone for prognostication; EEG required for confirmation
MRI	Extensive diffusion restriction 2–7 d post-ROSC supports poor prognosis	Same as AHA	Specifies the diffuse pattern of restricted diffusion should occur bilaterally across anterior and posterior circulation distributions and involve both cortical and subcortical areassss
CT	Reduced gray-white matter ratio supports poor prognosis; no specified timing	Same as AHA, but suggests evaluating at 72 h post-ROSC	Recommends evaluating for diffuse loss of gray-white differentiation and sulcal effacement at ≥48 h post-ROSC
EEG	Burst-suppression is a reliable predictor; recommended ≥72 h post-ROSC	Burst-suppression is reliable; suppressed background with or without periodic discharges is moderately reliable; recommends >24 h post-ROSC	Same as AHA; also considers suppressed background (± periodic discharges) at ≥72 h a moderately reliable predictor

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Table 1
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Guidelines	AHA 2020 Guidelines	ERC-ESICM 2021 Guidelines[1]	NCS 2023 Guidelines
Somatosensory evoked potentials (SSEP)	Evaluate ≥24 h post-ROSC	Same as AHA	Recommends delaying SSEP evaluation until ≥48 h post-ROSC
Serum biomarkers (NSE)	High/increasing NSE within 72 h post-ROSC supports poor prognosis	Same as AHA	Cautions against using NSE due to lack of validated threshold and high FPR
Indeterminate prognosis	No specific recommendation	Recommends extended observation if aligned with patient's goals of care	Strongly supports prolonged observation in uncertain cases

[1] *Abbreviations*: AHA, American Heart Association; ERC-ESICM, European Resuscitation Council and European Society of Intensive Care Medicine; NCS, Neurocritical Care Society.

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the binary question, "*Will this patient survive neurologically intact?*," clinicians should be asking instead: "*How long will recovery take, and to what extent will specific functions be regained?*" and "*What level of disability would be considered meaningful or acceptable for this individual?*." This shift in perspective is particularly important when navigating prognostic uncertainty[9] and reflect the bias of attribute substitution, when using a simpler, related question when trying to tackle a complex problem.[10]

Cognitive biases

While integrating multiple predictive modalities improves prognostic accuracy and reduces uncertainty, it also increases complexity and the risk of cognitive biases driven by heuristics. Neuroprognostication is fraught with uncertainty, from limitations of current prognostic tools,[11] methodology used in neuroprognostic studies,[12] and cognitive biases underlying systematic errors inherent to the process of outcome prediction.[10] Most patients who remain comatose after cardiac arrest ultimately die from neurologic causes: approximately 10% to 20% progress to brain death,[13–15] while the remaining 80% die following withdrawal of life support based on the perceived poor neurologic prognosis.[16,17] Even in the context of clinical trials, deaths related to withdrawal of life support occur prematurely within 72 hours from ROSC.[11,18]

The self-fulfilling prophecy bias is pervasive in neuroprognostic studies, perpetuating the overinflated prediction performance of tools being investigated, when the findings from such tools are used in clinical practice to inform end-of-life decisions.[10,12] Acknowledging the role of heuristic judgment is critical in outcome prediction, as withdrawing life support based on an inaccurately perceived poor prognosis can lead to irreversible consequences. Health care providers are better at predicting 6-month mortality than neurologic outcomes[19]; this can also reflect self-fulfilling prophecy bias, reinforced heuristic judgment, and attribute substitution bias.

Timing and availability of prognostic tools

The predictive performance of various tools for estimating favorable or unfavorable outcomes varies widely.[20,21] Ideally, neuroprognostication should incorporate several modalities of tests; however, this is far from the reality: in a study utilizing administrative data, fewer than 10% of patients had at least one and only 2% had at least 2 prognostic tests.[22] A great threat to neuroprognostication is the limited access to recommended tools, which in turn leads to reduced familiarity and potential discomfort with their use and interpretation of findings creating a vicious cycle. The limited access to these tools, coupled with variability in how each provider conducts and interprets the available tests, presents significant risks that must be carefully considered. Future guidelines should account for variations in access to these modalities and provide alternative approaches to ensure equitable and reliable prognostication.

Another important challenge is the variability in the timing of assessments and prognostic conclusions. The timing of testing for neuroprognostic tools depends on each tool and on the intent for maximizing its yield; this is determined often by avoiding the effect of confounding (eg, temperature and sedatives effect) or neurophysiologic stunning from anoxic depolarizations. The ideal timing for testing also hinges on the intent for each specific tool: If capturing the impact of early injury from primary insults (thus, early timing for testing) or capturing the overall burden of HIBI after the cascade of secondary injury is completed (ie, delayed after 48–72 hours from cardiac arrest). Providers report favoring accuracy of predictors over timeliness of prognostic impressions; in fact, the highest false positive rate deemed acceptable among practitioners who perform neuroprognostication in hypoxic-ischemic encephalopathy is just 0.1%.[23] Conversely, there is a concerning trend of clinicians disclosing premature prognostic

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impressions in practice—often before the guideline-recommended minimum of 72 hours[18,24–26]—and relying on tools that carry an unacceptably high false positive rates (FPR; anchoring effect) or are used outside their optimal time window.[25]

Many threats to the accuracy of neuroprognostication may coexist and have a compounding effect—patients for whom prognostic impressions were premature, are also less likely to have more than one prediction tool used, or the involvement of a neurology consultant.[22,26] These findings reinforce the importance of providers anchoring their practices on evidence-based guidelines and refraining from overinflating the value of anecdotal experiences and ingrained clinical practices. Avoiding overconfidence and identifying knowledge gaps is crucial in mitigating biases and improving neuroprognostication accuracy.

Framework of Neuroprognostication

The process of neuroprognostication builds on the priority pillars depicted in **Fig. 1** to incorporate them into 5 key steps that follows ROSC as illustrated in **Fig. 3**A: (1) evaluating the patient's neurologic state; (2) assessing the extent of neuronal injury using a multimodal approach combining methods that assess for direct evidence of structural damage and surrogate markers of injury using neurophysiologic tests and clinical examination findings as summarized in **Figs. 2** and **3**B; (3) determining cerebral reserve and assessing cerebral resilience; (4) understanding the definition of meaningful recovery from the perspective of the patient; and (5) effectively communicating

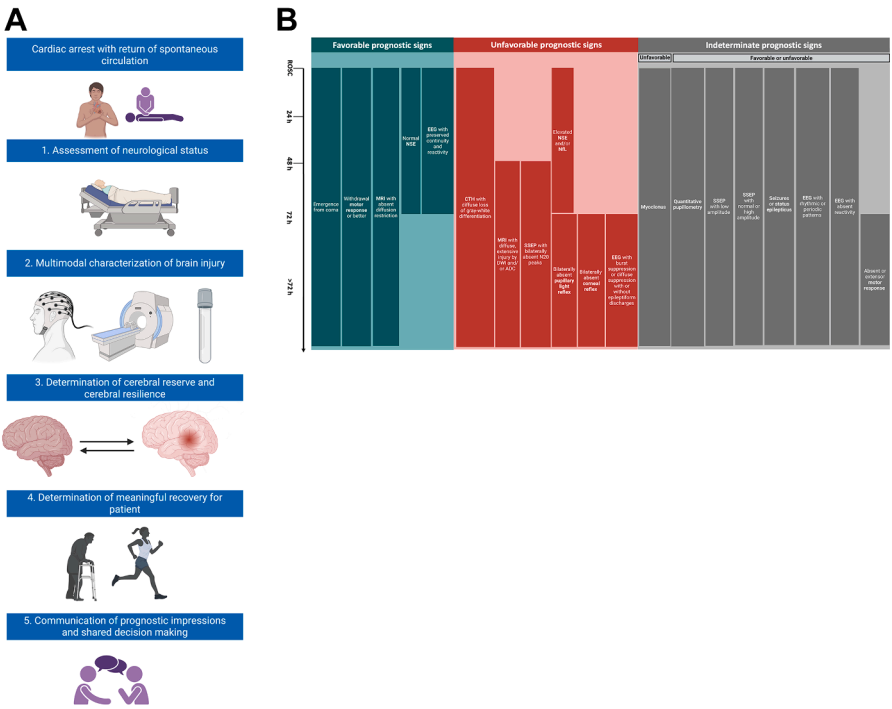
A
Cardiac arrest with return of spontaneous circulation
1. Assessment of neurological status
2. Multimodal characterization of brain injury
3. Determination of cerebral reserve and cerebral resilience
4. Determination of meaningful recovery for patient
5. Communication of prognostic impressions and shared decision making
B
Favorable prognostic signs
Unfavorable prognostic signs
Indeterminate prognostic signs
Unfavorable
Favorable or unfavorable
ROSC
24 h
48 h
72 h
>72 h
Emergence from coma
Withdrawal motor response or better
MRI with absent diffusion restriction
Normal NSE
EEG with posterior continuity and reactivity
CTH with diffuse loss of gray-white differentiation
MRI with diffuse, extensive injury to DWI and/or ADC
SSEP with bilaterally absent N20 peaks
Elevated NSE and/or NfL
Bilaterally absent pupillary light reflex
Bilaterally absent corneal reflex
EEG with burst suppression with or without epileptiform discharges
Myoclonus
Quantitative pupillometry
SSEP with low amplitude
SSEP with normal or high amplitude
Seizures or status epilepticus
EEG with rhythmic or periodic patterns
EEG with absent reactivity
Absent or inferior motor response

Fig. 3. (*A*) Key steps of neuroprognostication. (*B*) Timeline of multimodal approach to neuroprognostication. ADC, apparent diffusion coefficient; CTH, CT head; DWI, diffusion-weighted imaging; EEG, electroencephalography; NfL, neurofilament light chain; NSE, neuron-specific enolase; SSEP, somatosensory evoked potentials.

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prognostic impressions with the patient's family. Definitive prognostic impressions should be delayed until sufficient time has elapsed to account for potential confounders and the characterization of a trajectory (eg, serial examinations are captured following mitigation of confounding factors).

Assessment of neurologic status

Consciousness can be defined by its 2 main components: (a) "wakefulness" which is characterized by behavioral or electrophysiological indicators of arousal; and (b) "awareness" which is identified through responses to internal or external stimuli. Demonstration of awareness is a key point in the trajectory of brain injured patients, most commonly through the ability to follow commands. DoC are conventionally classified into 3 categories.

1. Comatose state: Unresponsive; complete lack of awareness.[27]
2. Unresponsive wakefulness syndrome: Wakeful but unresponsive.[28]
3. Minimally conscious state (MCS): Altered consciousness; minimal but definitive evidence of awareness of self or surroundings.[29] MCS can be further subdivided into MCS + or MCS– based on the presence or absence of complex behaviors, with emergence from MCS, defined as the recovery of functional communication or object use.[30]

Consciousness is primarily assessed through the neurologic examination, therefore, relying on the examiner's expertise. Distinguishing reflexive behaviors from subtle and inconsistent intentional movements is difficult, even for experienced clinicians. In a study of 137 patients with disorder of consciousness, more than 1 in 3 patients diagnosed with a wakeful unresponsive state had in fact some preservation of awareness when assessed using the Coma Recovery Scale-Revised[31] rendering them in a MCS. In another study, 1 in 5 patients had electrophysiologic or functional neuroimaging signs of awareness despite lack of corresponding behavioral responses, a finding now commonly referred to as cognitive motor dissociation or "covert consciousness."[32] Commonly used scales for evaluation of coma such as the Glasgow Coma Scale (GCS) and Full Outline of Unresponsiveness Score (FOUR) are in fact crude examinations prone to missing subtle signs of awareness. Emerging technologies provide insights into neuronal activity patterns indicative of consciousness not apparent through traditional examination alone, warranting a shift from rigid classification schemes to a dynamic continuum model of consciousness. This is important as patients with some preservation of awareness such as in cognitive motor dissociation represent a distinct subgroup with a more favorable recovery trajectory compared with those who remain in unresponsive wakefulness state.

Assessment of neuronal injury

In the seconds to minutes following cardiac arrest, a cascade of pathophysiological mechanisms triggered by anoxic depolarizations and calcium influx lead to programmed cell death that is known as "primary brain injury." Following ROSC, ongoing "secondary brain injury" ensues due to oxidative stress and reactive oxygen and nitrogen species, mitochondrial dysfunction, impaired autoregulation, and microcirculatory failure or "no-reflow," which can continue for hours to days. The overall burden of HIBI is comprised by both primary and secondary injury[33]; resilience to primary insult does not necessarily translate to resilience to secondary insults and at present, it is impossible to predict the magnitude of injury burden based on the severity of insults. Most neuroprognostic tools center on the evaluation of HIBI burden directly or indirectly (see **Fig. 2**).

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Direct evidence of cerebral injury

Neuroimaging. *Goal:* Neuroimaging is used to demonstrate the extent of HIBI without the confounding effects from sedation, metabolic derangements, and temperature.

Computed Tomography Imaging *Current Evidence:* The most studied method for HIBI quantification on computed tomography (CT) is gray-white matter ratio (GWR)[34]; however, evidence arises mainly from out-of-hospital cardiac arrest and predominantly within 24 hours from ROSC. The prognostic performance of GWR as a predictor of unfavorable outcomes increases when imaging is delayed due to increased sensitivity, likely from the ability to capture secondary injury.[35] Most data on GWR are derived from retrospective observational studies with various methods for calculation, imaging protocols, timing of imaging acquisition, and thresholds for best prognostic performance. The most recent prospective study demonstrated specificities of 100% for all GWR models, and sensitivities ranging from 30% to 41%, yielding the automated method area under the curve (AUC 0.84) when using a cut-off less than 1.10.[35]

Advantage: CT is widely available and is often used to evaluate cerebral edema in addition to gauging cerebral reserve through evaluation of parenchyma volume, areas of encephalomalacia or prior injury, burden of microvascular or white matter disease.

Disadvantage: The most reliable and objective measure of HIBI is GWR, which is not performed routinely in clinical practice. Visual assessment alone is subject to significant inter-rater variability.[36,37]

Recommendation: Diffuse loss of gray-white differentiation, ideally using quantitative methods, is helpful characterizing HIBI burden as early as within 2 hours from ROSC; however, delayed imaging is needed to capture overall burden of injury. There is insufficient evidence on GWR to support its use in predicting patients with a favorable outcome.[6]

MRI *Current Evidence:* Conventional MRI sequences used to detect HIBI include diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC). In DWI sequences, the degree of brain injury is characterized by the restriction in diffusion of water across the bilateral cortex and deep gray matter as represented through the image intensity. This restriction in water diffusion representing cytotoxic edema can be quantified through reporting of brain volumes with ADC below specific thresholds (650×10^{-6} mm^2/s or 450×10^{-6} mm^2/s). Other less studied sequences have lack validation and are not recommended by guidelines. Most data are derived from observational studies with significant heterogeneity on imaging protocols, subjective definitions for HIBI burden, different thresholds and regions of interest, and timing of assessments and outcomes.

Advantage: MRI provides more granular evaluation of structural injury with a higher sensitivity for detection than CT, particularly in the posterior fossa and brainstem.

Disadvantage: Several factors restrict the use of MRI, including incompatible metal devices and medical instability in critical care patients. Moreover, conduction of MRI is time-consuming, and it may not be readily available in many facilities. Qualitative assessments also have high inter-rater variability, and quantitative assessments are not widely performed in clinical practice.

Recommendation: Extensive areas of restriction on DWI or ADC when performed within 2 to 7 days after ROSC have been associated with unfavorable outcomes.[5,20] Reviewing areas of injury can be helpful in predicting specific corresponding deficits (eg, cortical blindness and sensory ataxia when extensive primary sensory cortex is involved) and discussing the recovery journey with surrogates. Conversely, the absence of extensive injury on MRI can be helpful in identifying patients with low HIBI burden.[6]

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Biomarker-based Assessment. *Goal:* Chemical biomarkers of neuronal injury are used to assess structural HIBI without the confounding effect of temperature, sedating medications, and/or toxic-metabolic insults.

Current Evidence: The quantification of serum biomarkers in HIBI has explored the role of NSE, glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), tau, ubiquitin carboxyl hydrolase L1, and serum calcium binding protein 100β (S-100B); each biomarker has distinct kinetics that influence temporal trends and optimal testing time and interpretation. The most widely studied and used in practice, NSE, is a biomarker of neuron cell-body injury, and has been demonstrated to remain elevated for up to 5 days after ROSC after its peak at 48 to 72 hours due to its half-life of 24 to 30 hours.[38,39] A systematic review of 86 biomarker studies found that NfL, a marker of white matter injury and axonal damage, had the highest predictive value for unfavorable prognosis with an AUC of 0.92 (95% CI, 0.84–0.97).[40] However, large-scale prognostic studies are needed before their use can be adopted widely.[41–43]

Advantages: Chemical biomarkers lack the influence of common confounders such as sedatives, and can be easily evaluated in studies that blind the clinical team to their results (therefore, mitigating confirmation biases). Its use.

Disadvantages: Heterogeneity of studies including type of biomarker, assay used, timing of assessments, and thresholds for evaluation of prognostic performance leads to significant imprecision in data; therefore, no specific recommendations can be made on the best modality and how they should be used. Most biomarkers are not available in clinical practice outside of research realm, or whenever available, their turn-around time of several days hinder its utility during the first week of hospitalization. Additionally, NSE, the most commonly used biomarker in HIBI, is susceptible to confounders by extra-cerebral sources such as neuroendocrine tumors or hemolysis; the latter is particularly relevant in patients with extracorporeal membrane oxygenation. The most promising biomarker from recent literature, NfL, requires ultra-sensitive assays due to limited diffusion through blood-brain barrier.[44]

Recommendation: Very high levels (insufficient data precludes specific cut-offs) of NSE and NfL within 72 hours from ROSC support significant structural HIBI. Conversely, sustained normal levels of NSE (<17 μg/L),[6,21,45] NfL, and GFAP within 72 hours from ROSC may be helpful in identifying patients without significant HIBI burden.[21]

Indirect evidence of neuronal functional impairment

Goal: Electrophysiologic tests and components of clinical examination supplement the detection of structural injury by providing additional evidence of neuronal impairment through evaluation of its function or connectivity.

Neurologic Examination. *Goal:* Components of the coma examination yield information on neuronal dysfunction from HIBI at a level that could indicate significant disability.

Current Evidence: A thorough examination provides insights into a patient's neurologic status by evaluating brainstem reflexes, motor responses, and overall level of consciousness. The lack of pupillary light responses and corneal reflexes (alone or in combination) is the most reliable neurologic finding in predicting an unfavorable prognosis with very low FPR when demonstrated at 72 hours or more from ROSC[20] in the absence of confounders; however, the preservation of these reflexes do not reliably predict good prognosis.[6,21] Findings of quantitative pupillary light reflex of 0% and Neurologic Pupil Index $\leq$2 within[46,47] have demonstrated high specificity for predicting unfavorable outcomes even earlier than 72 hours from ROSC; higher thresholds of reactivity as early as within 24 hours from ROSC maintained high specificity.[48,49] The finding of absent motor responses or posturing (flexion or

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extension) to noxious stimulation has unacceptably high FPR to be used as a predictor of unfavorable outcomes[20]; however, withdrawal motor responses or better have been associated with favorable outcomes.[6,21,45] Myoclonus, once considered pathognomonic for agonal cerebral injury after cardiac arrest, has been reappraised as an unreliable neuroprognostic finding[5,20]; this is likely due to different electroclinical phenotypes which also include early Lance-Adams syndrome.[50,51]

Advantages: Wide availability and relatively low need for advanced expertise for most components of the neurologic examination are the main advantages of the neurologic examination as a prognostic tool. Infrared pupillometry adds reproducible, objective, and quantitative information on pupillary light responses.[52,53]

Disadvantages: Neurologic examination findings are the most susceptible to confounding by temperature, sedatives, neuromuscular blockade, and neuronal stunning from anoxic depolarizations. Reliability of findings hinge upon the quality of assessments, and subjectivity of examination limits its accuracy.[54] Pupillometry can detect reactivity in up to one-third of pupils deemed unreactive by naked eye[53]; however, their limited availability and lack of consensus on specific timing for assessment and ideal thresholds hinders its use. Given its wide availability leading to its ubiquitous use in neuroprognostication for decades, neuroprognostic studies evaluating the prediction performance of findings from neurologic examination are profoundly impacted by self-fulfilling prophecy bias.

Recommendation: Bilateral absence of pupillary light response demonstrated by traditional examination or through pupillometry and bilateral absence of corneal reflexes when demonstrated at 72 hours or later from ROSC returns to normothermia and upon discontinuation of confounding medications are robust predictors of unfavorable outcomes.[5,20] Absent or reflex-only motor responses should not be used as a reliable predictor of unfavorable outcomes[5]; however, favorable motor responses can help predict patients with a higher chance for functional recovery.[6] Undifferentiated myoclonus should not be used as a predictor of unfavorable outcomes.[5]

Electroencephalography. *Goal:* Electroencephalography (EEG) demonstrates neuronal dysfunction with high temporal and spatial resolution in postcardiac arrest syndrome.

Current Evidence: The prediction performance of several findings on EEG has been evaluated for detecting favorable and unfavorable trajectories following cardiac arrest. Derived from a research protocol,[55] patterns were classified into highly malignant (predicted to have FPR, approaching 0%), malignant (FPR <5%), or benign (associated with favorable outcomes)—while intuitively helpful in research, there are inconsistencies in practice and in the overall literature with the use of this nomenclature. The findings of burst suppression and diffuse suppression, with or without epileptiform features, have been consistently associated with very low FPR and are considered the most reliable EEG findings as predictors of unfavorable outcomes, particularly when following the American Clinical Neurophysiology definitions and in the absence of sedatives.[20] Seizures, status epilepticus, and other epileptiform findings such as rhythmic and periodic patterns—all considered to be signs of hyperexcitability in HIBI—have been associated with unfavorable outcomes; however, their prediction performance vary widely.[20] In such cases, the concurrent presence of preserved background continuity and reactivity helps identifying patients with a higher chance for regaining consciousness in patients who have hyperexcitable findings.[56] In fact, the presence of these predictors within 72 hours from ROSC is also helpful in the absence of seizures and/or rhythmic or periodic patterns.[6] While preserved reactivity has a role predicting favorable outcomes, its absence has carried unacceptably high FPR when predicting unfavorable outcomes.[20]

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Advantages: EEG is one of the most relied upon neuroprognostic tool[25] for its wide availability, temporal resolution, and versatility in providing key information that helps detect favorable and unfavorable trajectories. While continuous EEG is much less accessible to many institutions, repeating short studies at regular intervals account for temporal evolution of findings.

Disadvantages: EEG findings should be interpreted with careful consideration for the presence of confounding factors such as sedating medications, temperature, and their evolution over time postarrest.[57] Furthermore, reporting of relevant findings depend on the interpretation of the encephalographer and their expertise in relaying relevant prognostic information in this context.[58,59] Reliability for reactivity is contingent upon standards for its assessment, which is highly variable across centers; proposed consensus on the reactivity testing are highly demanding and may not be realistic for many centers.[60]

Recommendation: The American Clinical Neurophysiology Society's standardized nomenclature for reporting EEGs should be followed when reporting studies in cardiac arrest survivors.[6,61,62] Persistent burst suppression or suppression of background, with or without generalized periodic discharges are considered the most reliable EEG predictors of unfavorable outcomes when present within 72 hours from ROSC. Preserved continuity and reactivity within 72 hours are useful predicting a favorable trajectory.[6]

Somatosensory Evoked Potentials. *Goal:* Somatosensory evoked potentials (SSEP) evaluate the integrity of sensory pathways at peripheral, spinal, subcortical, and cortical levels; when stimulating the median nerve, the finding of disrupted thalamocortical pathway indicates a significant potential for severe disorder of consciousness.

Current Evidence: During SSEP testing, electrical stimulation is applied to the median nerve at the wrist while recording the evoked potentials from scalp electrodes placed over the contralateral primary somatosensory cortex.[63] The bilateral absence of N20 waves (primary somatosensory cortex) without disruption in the proximal electrodes has been associated with unfavorable outcomes at various timepoints, with the highest reliability and near zero FPR at 48 hours or later after ROSC.[20] While bilaterally present N20 waves are unreliable, predicting favorable outcomes, the actual amplitude of the N20 waves might hold such potential; however, the literature is imprecise to allow for specific threshold or technique to be recommended.[6,21] Likewise, lower amplitudes have been associated with unfavorable outcomes with variable proposed cut-offs and timing for testing.[64,65]

Advantages: Despite being a neurophysiologic test, SSEPs are less likely to be significantly affected by common confounding factors in the postcardiac arrest course.

Disadvantages: Although SSEPs are not affected by sedatives to the same extent as EEG, they are not widely available or preferred,[25] limiting their use. Interpretation may also have subjective variation due to the presence of artifacts or technically insufficient recordings[66,67]; neuromuscular blockade can help mitigate myogenic artifact.[68]

Recommendation: Bilateral absence of cortical latencies (N20 waves) on median nerve stimulation SSEP is a reliable predictor of unfavorable outcomes when obtained at 48 hours or later from ROSC.

Cerebral reserve and resilience

Not every brain has the capacity to withstand and recover from cerebral injury to the same extent. A young, healthy person with a well-developed brain, abundant synapses and intact neuroplasticity is more likely to recover compared with an individual

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affected by age-related degeneration, structural abnormalities, or prior pathologies. The concepts of cerebral reserve and cerebral resilience are important in understanding these differences, although they are still subjectively defined. Cerebral reserve might be termed as an injured brain's ability to compensate for or adapt to damage or loss of neurons while maintaining comparable functionality. Cerebral resilience, on the other hand, refers to the brain's inherent "resistance" or "tolerance" to injury. Preclinical data suggests that prior exposure to nonlethal ischemic insults induces "ischemic tolerance" by developing survival responses that later allow it to withstand more severe ischemic insults without significant functional incapacitation.[69]

Assessing cerebral reserve and resilience through a comprehensive evaluation can help tailor findings from neuroprognostic testing into the specific scenario at hand, and personalize predicted trajectories for functional recovery.

Understanding patient goals and perspectives

"Good" or "bad" outcomes as defined in clinical research based on dichotomized scales fail to capture the deeply personal and nuanced nature of "meaningful" recovery. Advance directives, though helpful in guiding decisions, are frequently unavailable.[70] Determining what constitutes an acceptable journey or functional status for each patient is essential to define therapeutic targets and the boundaries of restorative care. For patients who are unable to communicate their goals and wishes, this responsibility falls upon surrogates, who may feel unprepared or emotionally overwhelmed by the weight of this task.

Surrogate decision-making is challenging and requires individuals to process complex medical information while striving to uphold the patient's wishes, all while navigating their own emotions, biases, fears, and high levels of stress and anxiety—all of which can impact judgment.[71] Surrogates and clinicians alike may unintentionally assume that severe disability equates to a poor quality-of-life, a bias known as "ableism."[72] Notably, there is a "disability paradox" where individuals living with significant disabilities often report a satisfactory or even high quality-of-life, despite external perceptions to the contrary.[73]

Before conveying definitive prognostic impressions, clinicians must explore what meaningful recovery would mean for the patient through the lens of the patient's life. This requires an effort to understand the individual from a humanistic lens before the injury, characterizing what brings them joy and fulfillment, and what their aspirations and values were and could still be. By gaining a deeper understanding of the patient as a whole person, rather than reducing them to their current condition, clinicians can better align prognostic discussions with the patient's true values and guide decision-making.

Communicating prognostic impressions

Effective, timely, compassionate and longitudinal communication from the clinical team is paramount. Communication breakdowns remain a major source of stress and dissatisfaction, often stemming from a disconnect between what surrogates need and how clinicians convey prognostic information.[74] Surrogates seek compassionate, timely, and honest discussions, desiring numeric estimates of prognosis to help reduce uncertainty. Yet, many physicians are hesitant to provide exact probabilities, fearing that surrogates might misinterpret these figures or place undue weight on them. This discrepancy creates frustration for surrogates, who may struggle to navigate the uncertainty inherent in neuroprognostication.[75]

The key challenge is to balance a surrogate's preference for concrete numbers with the reality of prognostic uncertainty. While absolute certainty is not possible when

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predicting outcomes, clinicians can still provide transparent and structured discussions to guide decision-making. This includes acknowledging uncertainty honestly rather than avoiding it, as failure to do so may exacerbate surrogate distress. Clinicians should explain prognostic estimates within a broader context, contrasting best-case and worst-case scenarios. For example, a physician might frame the discussion as: "The best scenario, in approximately 10% of such cases, is that your loved one recovers enough to communicate and regain some mobility, but they may always need assistance with daily tasks. The worst-case scenario is that they remain dependent on all care and may not regain meaningful interaction. Most patients fall somewhere in between, but it's difficult to say exactly where."

Additional components that can improve the experience for surrogates and families include having adequate time to talk, receiving reassurances from the clinical team regarding the patient's comfort, and acknowledgment of their decision.[76,77] Improving communication in neuroprognostication requires more research into best practices, standardized training for clinicians, and decision-making support for surrogates.

FUTURE DIRECTIONS

Most neuroprognostication literature has focused on predicting unfavorable outcomes with a high specificity, lacking adequate sensitivity and perpetuating the unknowns for most patients without such predictors and whose prognosis is deemed indeterminate. Identifying patients with potentially meaningful recovery potential is important to allow for targeted interventions that expedite awakening and support ongoing life support. As updated guidelines start to incorporate predictors of favorable outcomes,[6] and new evidence supports the validity and precision of findings, neuroprognostic practices may experience a paradigm shift.

Incorporating advanced methods for the detection of consciousness and developing multimodal frameworks integrating functional neuroimaging[78–80] also hold the potential to pivot the field of neuroprognostication into precision medicine. The Neurocritical Care Society's Advanced Classification of Consciousness Endotypes (ACCESS) is an example incorporates neurologic examination, standard neuroimaging, and advanced neuroimaging to provide a dynamic and adaptable model of consciousness assessment.[81]

While the concepts of cerebral reserve and resilience are intuitive for most seasoned clinicians, they are profoundly understudied. Prevailing knowledge gaps in this area, including lack of objective definitions and methods for quantification of reserve and resilience, hinders its application in clinical practice and challenges its incorporation in guidelines. Future studies expanding the scope of these concepts and demonstrating the added value of this key variable into neuroprognostication algorithms hold promise in augmenting accuracy in the prediction of neurologic recovery trajectories.

Lastly, the integration of artificial intelligence and machine learning into neuroprognostication holds promise in the ability to identify patterns through processing of large multimodal datasets that traditional methods might overlook. However, it is essential to recognize that these systems can inadvertently amplify existing biases present in real-world data.[82]

SUMMARY

Neuroprognostication remains an inherently uncertain process due to the evolving nature of HIBI, the limitations of prognostic tools, and the wide spectrum of patient outcomes, ranging from full recovery to severe disability or death. However, this

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uncertainty does not diminish its profound implications for patients, families, physicians, and society. A comprehensive assessment of neurologic injury using multiple tools is essential, and so is an acceptance of the inherent unpredictability. Clinicians should adopt a patient-centered approach, engaging in honest and compassionate discussions that set realistic expectations without fostering false hope. Standardized guidelines for neuroprognostication can help reduce bias and enhance accuracy, though current recommendations are far from exhaustive and remain limited to the quality and applicability of available evidence. As research continues to refine prognostic tools and methodologies, it is crucial to remain anchored in the core ethical principle: decisions based on prognostic assessments must align with the patient's perspective on what constitutes meaningful recovery.

CLINICS CARE POINTS

- Neuroprognostication in cardiac arrest survivors is challenging due to the evolving nature of neurologic injury, limitations in current prognostic tools, self-fulfilling prophecy bias, and uncertainty in recovery trajectories.
- No single modality reliably predicts neurologic outcome with high sensitivity and a low false-positive rate; using multiple modalities improves prognostic accuracy and reduces bias.
- Understanding meaningful functional recovery requires a patient-centered approach rather than reliance on standardized scales, which do not capture individual preferences.
- The predictors of unfavorable outcomes that have demonstrated the best performance include bilaterally absent pupillary light and corneal reflexes $\geq$72 hours postarrest, bilaterally absent N20 waveforms on somatosensory evoked potentials $\geq$48 hours postarrest, suppressed background or burst suppression $\geq$72 hours postarrest on electroencephalography (EEG), reduced gray-white ratio on computed tomography, and diffuse hypoxic-ischemic injury on MRI performed between days 2 to 7 postarrest.
- Favorable outcome predictors include absent diffusion restriction on MRI within 2 to 7 days, preserved EEG reactivity and continuity within 72 hours postarrest, withdrawal motor response or better, and normal serum biomarker levels within 72 hours.
- It is of utmost importance for clinicians caring for postarrest patients to be well versed in guideline-recommended neuroprognostication methods, be aware of evolving data affecting current practices, and identifying goals of recovery from the patient's and surrogate's perspectives.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used GenAI in order to correct typos and grammar mistakes in the writing process of this article. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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DISCLOSURE

The authors have nothing to disclose.

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